K080564

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510(k) Summary of Substantial Equivalence
Aperio Technologies, Inc.
(ScanScope® XT System)

21 CFR 807.92(a):

21 CFR 807.92(a) (1):

Submitter's name and address:
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AUG 14 2009

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Date this 510(k) summary was prepared:
February 25, 2008, revised August 12, 2009

21 CFR 807.92(a)(2):

Trade Name of Device:	ScanScope® XT System
Regulatory Section:	21 CFR 864.1860 Immunohistochemistry reagents and kits
Classification:	Class II
Product Code:	NOT (microscope, automated, image analysis, operator intervention)

21 CFR 807.92(a)(3): Leally marketed predicate device to which substantial equivalence is claimed:

Predicate Device #1:	Automated Cellular Imaging System ("ACIS") and ACIS HER2 software application
Manufacturer:	ChromaVision Medical Systems, Inc.

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Predicate Device K#:	K032113
Predicate Device #2:	Applied Imaging Ariol™ with HER2 Application
Manufacturer:	Applied Imaging Corporation
Predicate Device K#:	K031715

21 CFR 807.92(a)(4): Description of the device that is the subject of this pre-market notification:

System: The ScanScope® XT System is an automated digital slide creation, management, viewing and analysis system. The system is comprised of a slide scanner instrument and a computer executing Spectrum™ software. The system capabilities include digitizing microscope slides at diagnostic resolution, storing and managing the resulting digital slide images, retrieving and displaying digital slides, including support for remote access over wide-area networks, providing facilities for annotating digital slides and entering and editing metadata associated with digital slides, and facilities for image analysis of digital slides, including the ability to quantify characteristics useful to Pathologists, such as measuring and scoring immunohistochemical stains applied to histology specimens, such as Dako HerceptTestTM which reveals the presence of proteins such as Human Epidermal growth factor Receptor 2 (HER2), which may be used to determine patient treatment for breast cancer.

Hardware Operation: The ScanScope® digital slide scanner creates seamless true color digital slide images of entire glass slides in a matter of minutes. A high numeric aperture 20x, as found on conventional microscopes, is used to produce high-quality images. (When the 2X magnification changer is inserted, the effective magnification of the images is 40x.) The ScanScope® XT employs a linear-array scanning technique that generates images free from optical aberrations along the scanning axis. The result is digital slide images that have no tiling artifacts and are seamless.

Software Operation: The Spectrum™ software is a full-featured digital pathology management system. The software runs on a server computer called a Digital Slide Repository (DSR), which stores digital slide images on disk storage such as a RAID array, and which hosts an SQL database that contains digital slide metadata. Spectrum includes a web application and services which encapsulate database and digital slide image access for other computers. The Spectrum server supports the capability of running a variety of image analysis algorithms on digital slides, and storing the results of analysis into the database. Spectrum also includes support for locally or remotely connected image workstation computers, which run digital slide viewing and analysis software provided as part of Spectrum.

Overview of System Operation: The laboratory technician or operator loads glass microscope slides into a specially designed slide carrier with a capacity of up to 120 slides. The scanning process begins when the operator starts the ScanScope® scanner and finishes when the scanner has completed scanning of all loaded slides. As each glass slide is processed, the system automatically stores individual "striped" images of the tissue contained on the glass slide and integrates the striped images into a single digital slide image, which represents a histological reconstruction of the entire tissue section. After scanning is completed, the operator is able to view and perform certain analytical tests on the digital slides.

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21 CFR 807.92(a)(5): Intended use and labeled indications for use:

The ScanScope System is an automated digital slide creation, management, viewing and analysis system. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting and classification of tissues and cells of clinical interest based on particular color, intensity, size, pattern and shape.

The IHC HER2 Breast Tissue Tunable Image Analysis application is intended for use as an aid to the pathologist in the detection and semi-quantitative measurement of HER2/neu (c-erbB-2) in formalin-fixed, paraffin-embedded normal and neoplastic tissue.

The IHC HER2 Breast Tissue Tunable Image Analysis application is intended for use as an accessory to the Dako HercepTest™ to aid in the detection and semi-quantitative measurement of HER2/neu (c-erbB-2) in formalin-fixed, paraffin-embedded normal and neoplastic tissue. It is indicated for use as an aid in the assessment of breast cancer patients for whom HERCEPTIN® (Trastuzumab) treatment is being considered. Note: The IHC HER2 Breast Tissue Tunable Image Analysis application is an adjunctive computer-assisted methodology to assist the reproducibility of a qualified pathologist in the acquisition and measurement of images from microscope slides of breast cancer specimens stained for the presence of HER2 receptor protein. The accuracy of the test result depends upon the quality of the immunohistochemical staining. It is the responsibility of a qualified pathologist to employ appropriate morphological studies and controls as specified in the instructions for the HER2 reagent/kit used to assure the validity of the IHC HER2 Breast Tissue Tunable Image Analysis application assisted HER2/neu score. The actual correlation of the HER2 reagents/kits to Herceptin® clinical outcome has not been established.

21 CFR 807.92(a)(6): Technological characteristics:

The design, construction, energy source and other characteristics of the ScanScope® XT System candidate device are considered to be substantially equivalent to the relevant features of the predicate devices. A summary of the technological characteristics of the ScanScope® XT System candidate devices in comparison to the predicate devices follows:

Method of cell detection: The method of cell detection is by colorimetric pattern recognition by microscopic examination of prepared cells by size, shape, hue and intensity as observed by a computer-automated, microscopic digital slide scanner system and/or by visual observation by a health care professional.

System Components: The system components comprising the ScanScope® XT System candidate device are substantially equivalent to those in the predicate device; i.e., a computer-automated digital microscope slide scanner, computer, color monitor, and keyboard.

Energy Source: The electrical service is 100vAC – 240vAC, 50Hz/60 Hz, 2 amp, which is similar to the predicate device electrical service requirements.

21 CFR 807.92(b): 510(k) summaries for those pre-market submissions in which determination of substantial equivalence is also based on an assessment of performance data shall contain the following information:

21 CFR 807.92(b)(1): Brief discussion of non-clinical tests submitted, referenced or relied on in this pre-market notification:

There are no non-clinical tests submitted, referenced or relied on in this submission.

21 CFR 807.92(b)(2): Brief discussion of clinical tests submitted, referenced or relied on in this pre-market notification:

Comparison Studies

a. Method Comparison with predicate devices:

The substantial equivalence study was based on comparison of image analysis to conventional manual microscopy.

A total of one hundred and eighty (180) formalin-fixed, paraffin-embedded breast tissue specimens from two (2) clinical sites were used for this study; eighty (80) specimens at the first clinical site and one-hundred (100) specimens at the second clinical site.

Similar to the substantial equivalence study of the ACIS and Ariol™ systems, three (3) pathologists at each clinical site used two different methods of review, first using manual microscopy with a conventional light microscope and then using the ScanScope® XT System to provide raw system scores.

All specimens at the first and second clinical site were immunohistochemically stained using Dako in vitro diagnostic (IVD) FDA approved HerceptTest (P980018).

Clinical Site	Reagent	Number of Specimens	HER2 Score Distribution
1	Dako HerceptTest	80	Equal
2	Dako HerceptTest	100	Target Population

Three (3) different board-certified pathologists at each clinical site performed a blinded manual review of each glass slide using a conventional light microscope. The pathologists reported HER2 scores of 0, 1+, 2+ or 3+ for each of the reviewed glass slides.

Based on the manual microscopy average HER2 scores from the three pathologists, the glass slides used for this study provided the following HER2 score distribution.

HER2 Score	Clinical Site 1	Clinical Site 2	Total
0	25	20	45
1+	26	42	68
2+	13	25	38
3+	16	13	29
Total	80	100	180

HER2 Score Distributions for the two Clinical Sites.

All glass slides were scanned using a different ScanScope® XT instrument for each clinical site.

For each clinical site the image analysis algorithms were configured using automatic training of the scoring scheme parameters from a representative training data set of twenty (20) HER2 slides, using the scores from the same three pathologists. The slides were chosen to have equal HER2 score distribution.

Image analysis was run on each slide for each of the different sets of tumor regions outlined by the three pathologists, resulting in a separate image analysis score for each of the three pathologists. Image analysis was run in batch processing mode completely separated from the pathologists outlining the tumor regions to avoid influencing the pathologists in their choice of tumor regions. The image analysis algorithm reported the HER2 score 0, 1+, 2+ or 3+ for each of the digital slides.

Statistical analyses are provided for a trichotomous categorization of the HER2 scores combining 0 and 1+ and leaving 2+ and 3+ uncombined. Percentage Agreement (PA) along with an exact 95% Confidence Interval (CI) are presented overall for all trichotomous HER2 score categories combined and for each of the trichotomous HER2 score categories separately using a dichotomous outcome of that category vs. the two other categories. Tables for each of the methods (manual microscopy and image analysis) and comparison between the two methods are presented for the three different clinical sites and their pathologists.

	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	91.3%	(82.8, 96.4)	77.5%	(66.8, 86.1)	76.3%	(65.4, 85.1)
Clinical Site 2	84.0%	(75.3, 90.6)	82.0%	(73.1, 89.0)	90.0%	(82.4, 95.1)

Manual Microscopy - Inter-Pathologists - Agreements.

	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	91.3%	(82.8, 96.4)	92.5%	(84.4, 97.2)	88.8%	(79.7, 94.7)
Clinical Site 2	85.0%	(76.5, 91.4)	94.0%	(87.4, 97.8)	87.0%	(78.8, 92.9)

Image Analysis - Inter-Pathologists - Agreements.

	Pathologist 1 v 2		Pathologist 1 v 3		Pathologist 2 v 3	
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	87.5%	(78.2, 93.8)	87.5%	(78.2, 93.8)	80.0%	(69.6, 88.1)
Clinical Site 2	90.0%	(82.4, 95.1)	79.0%	(69.7, 86.5)	88.0%	(80.0, 93.6)

Manual Microscopy vs Image Analysis – same Pathologist - Agreements.

The percent agreements between the pathologists' manual microscopy and Image Analysis ranged from 76.3% to 90.0% with confidence bounds from 65.1% to 95.1%; the inter-pathologists agreements for manual microscopy ranged from 65.0% to 91.3% with confidence bounds from 53.5% to 96.4%.

The inter-pathologists agreements for Image Analysis ranged from 85.0% to 94.0% with confidence bounds from 76.5% to 97.8%; the inter-pathologists agreements for manual microscopy ranged from 79.0% to 91.3% with confidence bounds from 69.6% to 96.4%.

Note that these image analysis results were obtained by having the Pathologists choose and outline a representative set of tumor regions anywhere on the entire slide, completely blinded from each other, and blinded from the image analysis results (there was no influence on the Pathologists in their choice of the tumor regions).

Analytical Performance:

a. Precision/Reproducibility:

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The precision of the ScanScope® XT System was determined in a suite of intra-run/intra-system, inter-run/intra-system and inter-systems studies. Eight (8) HER2 slides from the comparison study were selected to provide two slides in each of the HER2 score classes 0, 1+, 2+ and 3+ based on the average HER2 score from the three pathologists in the comparison study.

Intra-day/intra-system: The slide scores provided by Image Analysis over ten (10) consecutive scans were analyzed for all eight (8) HER2 slides. The data show perfect agreement (100%) for the calculated HER2 scores across all runs.

Inter-day/intra-system: The slide scores provided by Image Analysis over twenty (20) scans on different days were analyzed for all eightHER2 slides. The data show perfect agreement (100%) for the calculated HER2 scores across all runs.

Inter-system: The slide scores provided by Image Analysis over ten (10) consecutive scans on three (3) different ScanScope® XT instruments were analyzed for all eight (8) HER2 slides. These data show perfect agreement (100%) for the calculated HER2 scores across all systems and across all runs.

The **intra-Pathologist** precision was analyzed for conventional manual microscopy and image analysis. The variation of the image analysis due to the intra-Pathologist variability was also used to put the system variations evaluate in the intra-run/intra-system, inter-run/intra-system and inter-systems studies into perspective.

The agreement between image analysis scores based on the tumor regions outlined by the Pathologist and manual microscopy scores could not be assessed properly as the data suggests that the manual microscopy scoring by the Pathologist reflects a lower scoring bias. Using the average manual microscopy scores from the three (3) Pathologists scoring the same slides in the comparison study as a reference, image analysis scores based on the tumor regions outlined by the same Pathologist provided a good agreement with only 5 outliers out of 40 scores (12.5%) and all 5 outliers could be linked back to the two (2) border line cases in the data set - slide #4 with a mean of 9.3% cumulative percentage of 3+, 2+ and 1+ cells and slide #5 with a mean of 11.9% percent of 3+ cells. This study shows a good example how image analysis can help Pathologists with the standardization of the scoring.

Placing the pathologist variations into perspective enables comparison of intra-pathologist variations to inter-pathologist variations. These data show an average Standard Deviation and Range for all percentages of 3+ cells, cumulative percentages of 3+ and 2+ cells and cumulative percentages of 3+, 2+ and 1+ cells combined over all slides of 2.7% SD and 3.9% Range for the intra-pathologist variations (n=5) and 10.03% SD and 11.74% Range for the inter-pathologist variations (n=3). This shows that the variations introduced by a single pathologist by outlining different tumor regions from one read to another is 3x to 3.7x smaller than the variations introduced by different pathologists outlining different tumor regions. The highest variations are introduced by inter-pathologist variations, which still yield an excellent percent agreement between 87% - 97.5% in the comparison study in terms of the clinical relevant negative (0 and 1+) vs. positive (2+ and 3+) HER2 scores.

Algorithm Training Set: 100 HER2 slides from clinical site 1 were stratified into 0, 1+, 2+ and 3+ classes based on the average HER2 score provided by three pathologists using manual microscopy.

Three different algorithm training and evaluation runs were conducted. Each time, the 100 slides were separated into a training data set and an evaluation data set. The training data set consisted of 5 slides for each 0, 1+, 2+ and 3+ HER2 class that were selected randomly from the available slides within the HER2 classes (stratified-random selection)—a total of 20 slides. The remaining 80 slides were used as the evaluation data set. The training data set was used to tune the IHC HER2 Breast Tissue Tunable Image Analysis application according to the procedure outlined in the previous sections of this chapter. The tuned HER2 image analysis application was then run on the 80 slides of the test data set using the tumor region outlines provided by three pathologists during the digital read in the substantial equivalence study. The inter-pathologists variations for manual microscopy and image analysis as well as the inter-method variations are reported as previously in the substantial equivalence study.

The agreements between the pathologists' manual microscopy and Image Analysis ranged from 75.0% to 88.8% with confidence bounds from 66.5% to 95.7%; the inter-pathologists agreements for manual microscopy ranged from 75% to 90% with confidence bounds from 66.5% to 96.6% and the inter-pathologists agreements for Image Analysis ranged from 86.3% to 92.5% with confidence bounds from 78.7% to 97.7%.

....End of 510(k) Summary....

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center – WO66-0609
Silver Spring, MD 20993-0002

Aperio Technologies, Inc.
c/o Mr. Jeff Ryberg
Director of Quality, Regulatory and Clinical
1360 Park Center Dr
Vista, CA 92081

AUG 14 2009

Re: k080564
Trade/Device Name: ScanScope™ XT System
Regulation Number: 21 CFR 864.1860
Regulation Name: Immunohistochemistry reagents and kits
Regulatory Class: Class II
Product Code: NOT
Dated: July 14, 2009
Received: July 16, 2009

Dear Mr. Ryberg:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed

predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of *In Vitro* Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

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Indication for Use

510(k) Number (if known): K080564

Device Name: ScanScope® System

Indication for Use:

The ScanScope System is an automated digital slide creation, management, viewing and analysis system. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting and classification of tissues and cells of clinical interest based on particular color, intensity, size, pattern and shape.

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Prescription Use __X__ (21 CFR Part 801 Subpart D) And/Or Over the Counter Use_____ (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Maria M Chan

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety
510(k) K080564